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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/050,249	03/30/98	OKAMURA H	OKAMURA=2B

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EXAMINER	
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ART UNIT	PAPER NUMBER
1646	22

DATE MAILED: 07/03/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No.	Applicant(s)	
	09/050,249	OKAMURA ET AL.	
	Examiner	Art Unit	
	Dong Jiang	1646	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *93-118* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *97* is/are allowed.

6)☒ Claim(s) *93-96,and 98-118* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *08/502,535* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

DETAILED OFFICE ACTION

The request filed on 5 June 2001 for a Continued Examination (RCE) under 37 CFR 1.114 is acceptable and a RCE has been established. An action on the RCE follows.

Applicant's amendment and formal drawings in paper No. 19, filed on 05 April 2001 are acknowledged and entered. Following the amendment, the claim 93 is amended, and the new claim 118 is added.

Currently claims 93-118 are pending and under consideration.

Formal Matters:

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: the Examiner is unable to find the written description or definition in the specification for the term "IGIF" and "IL-18" in the claims, such as claims 93-96, 100, 104, 107-110, 113-118.

New Matter Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 93-96, 100, 104, 107-110, 113-118 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants have not pointed out, nor can the Examiner locate, the basis in the specification for the newly introduced recitation of "IGIF" and/or "IL-18" in these claims.

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 93-118 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 93 and 118 are indefinite for using parentheses, such as "(IGIF, IL-18)". It is unclear whether "IGIF, IL-18" in the parentheses is part of the limitations of the claims, and if so, what limitation is imported by such. See, for example, line 3 of claim 93.

Claim 93 is further indefinite for the recitation that "and has an amino acid sequence of SEQ ID NO:2, wherein one or more amino acids are replaced ..." (starting lines 5 of the claim). It is unclear how a molecule having SEQ ID NO:2 can also have replacements, additions or deletions of amino acids in the same time.

The term "substantially the same" in claim 93 (line 4) is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim, and the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear how much similarity in the physiochemical properties is "substantially the same".

Claim 118 is further indefinite because it is not clear what "IGIF" is, as no structural or functional limitation recited, and the specification does not definite such. The metes and bounds of the claimed mAb specific to "IGIF" protein, therefore, cannot be unambiguously determined.

Claim 94 is incomplete for omitting essential elements. The claim is limited by a hybridization method under specific conditions. However, the claim does not recite the washing condition, which would effect the removal of nonspecific hybridization complexes, and is one of the most critical steps of the method.

The remaining claims are rejected for depending from an indefinite claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 93, 94, 96, 118, and the dependent claims 95, 98-117 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited in scope to a monoclonal antibody specifically recognizing a polypeptide of SEQ ID NO:2, wherein Xaa is Met or Thr, does not reasonably provide enablement for with claims to monoclonal antibodies to variants of SEQ ID NO:2 (as recited in claims 93, 94, 96), or any "interferon-γ inducing protein" (claim 118). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to [make and/or] use the invention commensurate in scope with these claims.

Enablement is not commensurate in scope with claims 93, 94, 96, 118, and the dependent claims 95, 98-117, which, given the broadest interpretation, read on antibodies directed against any or all possible polypeptides a) "having" an partial amino acid sequence of SEQ ID NO:2, and physiochemical properties recited in parts (1)-(3) of claims 93 and 96; b) encoded by "a cDNA which is hybridizable with a probe *having* the coding sequence shown in SEQ ID NO:1" (claim 94); or c) with IFN-γ inducing activity (claim 118). The specification discloses one specific sequence of IFN-γ inducing protein with SEQ ID NO:2, and a working example (Example 3-3) to generate monoclonal antibody specific to murine IFN-γ inducing protein (SEQ ID NO:2). The specification does not define structurally or functionally any variants of SEQ ID NO:2 besides two isoforms with Met or Thr at the residue 70, or any additional sequences as claimed (as "having" being used), or teach how to make the variants meeting the limitations of the claims, and how to *make* the full scope of the antibodies. Further, the variant polypeptides, as claimed (see a) – (c) above), would undoubtedly possess epitopes that are not SEQ ID NO:2. To the extent that the claims encompass antibodies that bind to epitopes not found in the particularly disclosed sequences, there is no written description of those epitopes. Therefore, the structure properties and use of the corresponding antibodies are not predictable. In the absence of a disclosed use of those antibodies non-specific to SEQ ID NO:2, the specification fails to enable the skilled artisan to *use* the full scope of the subject matter of the noted claims.

Due to the large quantity of experimentation necessary to determine the activity of a given variant of SEQ ID NO:2 or a IFN-γ inducing protein such that it can be determined how to

make the claimed antibody, and to determine the specificity of a mAb in order to use the claimed antibody, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, and the breadth of the claims which fail to recite particular sequence structures of the polypeptides, and also embrace antibodies with non-specific antigenecity to SEQ ID NO:2 as a result of a broad class of structural fragments and variants (as antigens), undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 93-96 and 98-117 remain rejected, and claim 118 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

With respect to claims 93-96 and 98-117, applicants amendment, argument, and pointed out relevant contents in the specification have been fully considered, but they are not persuasive. The newly amended independent claim 93 failed to make substantial changes upon the issues addressed in the Final office action, paper number 18, filed on 06 December 2000. Therefore, certain rejections from the last Final office action still apply.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The specification discloses *one* amino acid sequence with particularity, the murine IL-18 with SEQ ID NO:2, and two possible isoforms differing at a single amino acid location, the residue 70 (Met^{70} and Thr^{70}), and a monoclonal antibody, mAb M-1, specific to SEQ ID NO:2. No other variants or species of IFN-γ inducing protein, or antibodies thereof meeting the limitations of these claims were ever identified or particularly described.

The limitations of present claims 93-96 and 98-118 encompass significant structural dissimilarity as compared to the exemplified IFN-γ inducing protein with SEQ ID NO:2, and

have not been shown to correlate with the biological activity required by these claims. A skilled artisan would not be able to reasonably expect, for example, that a molecular weight of 19.5 kDa, a pI of 4.8, or a requirement for the presence of short subsequences affording *ca.* 30% overall identity with SEQ ID NO: 2 would correlate with the retention of biological properties characteristic of the murine IL-18 described in the disclosure. Additionally, a "IFN-γ inducing protein" (claim 118) may not share sequence similarity with SEQ ID NO:2, for example, IL-12. The Office, therefore, concludes that the two isoforms of SEQ ID NO: 2, differing by only a single amino acid, are not representative of all variants recited in claims 93-96 and 98-118, and that to the extent that those variants might possess epitopes not found on the two disclosed isoforms, and antibodies to such epitopes have not been described, thus that the disclosure does not convey to those skilled in the art that the inventors were in possession of the genera of antibodies to variants of a IFN-γ inducing protein at the time the application was filed.

Rejections Over Prior Art:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 93-118, and 118 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nakamura *et al.* (*Infect. Immun.* 61: 64-70, 1993; provided by the applicant).

The equivalent rejection was made in the previous office action filed on 06 October 1999 (paper No. 10), and the present rejection is the reinstatement of parts 7 and 8 of the previous

office action (please refer to these parts and, especially, page 7, line 19, to page 9, line 24). The relevant sections of the rejection from the previous office action are following:

"Because Nakamura describes the protein of original claim 1, including its biological activity, a monoclonal antibody specific for that protein is obvious under 35 U.S.C. § 103 as a matter of law, per counsel's express concession.

To the extent that Nakamura is ambiguous as to the molecular weight and to the extent that claim 1 cannot be fairly construed to read on a material which is said to exhibit a molecular weight outside the recited range, counsel's concession nonetheless weighs in favor of the conclusion that the genus of monoclonal antibodies specific for the Nakamura IGIF material is obvious under § 103. In addition to conceding the obviousness of a mAb to "the protein of claim 1," counsel stated in the reply of 14 February 1997 that "[t]echniques of raising monoclonal antibodies are well known" and that "[k]nowing the biological activity of such protein [as the protein of claim 1], one of ordinary skill in the art would have been motivated to make a monoclonal antibody for the purpose of immunoaffinity chromatography or for the purpose of blocking its activity. The techniques for doing so are well known." These concessions are generic in nature.

Because the 18-19 kDa IGIF is at the least a significant component of the 55/75 kDa material described by Nakamura (Okamura considers the possibility that Nakamura observed a multimer), a significant number of the antibodies within the genus conceded to be obvious in view of it would have recognized epitopes on the 18-19 kDa component. Furthermore, the prior art teaches the biological activity which counsel has conceded that it would have been obvious to block using a conventionally made monoclonal antibody, and the evidence of record indicates that the biological activity is associated with the 18-19 kDa component of the prior art material. It is therefore the examiner's determination that counsel has conceded the obviousness of the genus of monoclonal antibodies specific for the Nakamura IGIF and has further conceded that it would have been obvious to select from that genus the subgenus of antibodies capable of blocking the activity described in the prior art. Because the evidence of record indicates that such antibodies would meet all of the limitations of the instant claims, such claims are consequently unpatentable under 35 U.S.C. § 103.

The monoclonal antibodies conceded to be obvious, as discussed above, meet the limitations of claims 59, 60, 81, and 86, the latter claim notwithstanding the recited method of making. Because counsel has conceded that it would have been obvious to make a mAb for the purpose of immunoaffinity chromatography or for the purpose of blocking [an IGIF protein's] activity," the mAbs of claims 63, 82, and 87, and the corresponding methods of using them, to which claims 56, 67, 68, 74, 75, 84, and 88 are directed, have been conceded to be obvious. Because the only technique for making monoclonal antibodies known in the art (prior to having in hand a cDNA encoding one) necessarily involves the production of hybridomas and their cultivation to produce and recover the mAbs, the subject matter of claims 64, and 65 has equivalently been conceded to be obvious.

The subgenus of antibodies claimed in claim 61 does not patentably distinguish over the mAb of claim 59 because, as was appreciated in the art at the time of the invention, the great majority of hybridomas obtained in a conventional fusion elaborate IgG or IgM antibodies.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to label an IGIF-neutralizing mAb with an label conventionally known in the art, *e.g.*, an enzyme for an ELISA assay, because the artisan would have expected that the easily detectable mAb would be useful for detecting and quantitating the material for which it is specific. For essentially similar reasons, it would have been obvious to use such an antibody to detect or quantitate a protein having IGIF activity, such as the material described by Nakamura, because the artisan would have found it desirable to be able to do so, *e.g.*, to track the progress of a purification protocol. It further would have been obvious to do so in any format commonly employed in the art, such as ELISA, because the artisan would have expected to realize the recognized advantages of using such formats.

In producing a monoclonal antibody by conventional methodology, it would have been obvious to recover the antibody from a hybridoma culture using any conventional protein purification or manipulation techniques, such as affinity chromatography using an Ig-specific reagent (Protein A and the like) because such techniques were conventionally employed in the art at the time of the invention for the recovery of mAbs and were recognized to be advantageous for producing pure, concentrated immunological reagents.

In using the mAbs for immunoaffinity purification, it would have been obvious to purify a material having IGIF activity, such as the protein described by Nakamura, in a column chromatography format because that format was recognized in the art at the time of the invention as an efficient means for resolving and recovering proteins in immunoaffinity experiments. The artisan would have expected to recover an IGIF material having very high purity and with essentially complete recovery of activity because most biologically active proteins purified by immunoaffinity chromatography prior to the time of the invention could be so recovered following routine experimentation to ascertain effective parameters for the purification steps."

It has been proven that Nakamura's 55/75 kDa protein comprises the same molecule of 18-19 kDa IGIF (see the previous rejection). It would be obvious to make the monoclonal antibodies to a novel protein, such as Nakamura's, because it is well known in the art that antibodies are useful in facilitating further study and purification of the protein. For example, Boldain et al. (Monoclonal Antibodies For Cancer Detection And Therapy, page 20, 1985) teaches that it is relatively easy to make additional monoclonal antibodies to an antigen that has already been identified, and that one can screen with a two-site immunoradiometric assay using an available antibody to one determinant of the antigen and selecting for an antibody to another determinant of the same antigen (see the underlined lines).

Conclusion:

Claim 97 is allowable.

Advisory Information:

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 703-305-1345. The examiner can normally be reached on Monday - Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

David Romeo
Primary Examiner

DJ
6/25/01